AIR FORCE HEALTH STUDY

AN EPIDEMIOLOGIC INVESTIGATION OF HEALTH EFFECTS IN AIR FORCE PERSONNEL FOLLOWING EXPOSURE TO HERBICIDES

REPRODUCTIVE OUTCOMES
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EXECUTIVE SUMMARY

The Air Force is conducting a 20-year prospective study of the health of veterans of Operation Ranch Hand, the unit responsible for aerial spraying of herbicides in Vietnam from 1962 to 1971. The health of those veterans is compared to that of a group of other Air Force veterans who served in Southeast Asia (SEA) and who had no occupational exposure to herbicides. The study, called the Air Force Health Study (AFHS), is in its tenth year and is designed to determine whether exposure to the herbicides or their contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), has adversely affected the health, survival or reproductive outcomes of Ranch Hands.

This report summarizes the findings of an investigation of reproductive outcomes of the 791 Ranch Hands and 942 Comparisons for whom a dioxin level had been determined by August, 1991. These men have fathered 5,489 pregnancies including 4,514 live births. These men are a subset of all Ranch Hands (n=1,098) and Comparisons (n=1,549) who have fathered 8,263 pregnancies and 6,792 live births. All data in this report have been verified by review of birth certificates, newborn clinic records, health records and death certificates. The health status of each child was verified through the age of 18.

The analysis of birth defects in the baseline AFHS report, released in 1984, found that the Ranch Hand rate of reported pre-SEA defects was less than the Comparison rate and the Ranch Hand rate of reported post-SEA defects was greater than the Comparison rate. The baseline finding motivated the verification of conception outcomes and birth defects which are the subject of this report. Reanalysis using verified data also found similar results; however, additional analyses found no indication that these group differences were related to paternal dioxin levels. Furthermore, analyses within each of 13 categories of birth defects found no evidence that this finding was attributable to any specific category of anomalies.

This study is the first to combine a direct measurement of dioxin level with documented and verified reproductive outcomes in a population of sufficient size to provide a reasonable opportunity to detect possible associations between paternal dioxin levels and a range of common reproductive outcomes. This study has good statistical power to detect relative risks of 2 for common birth defects such as musculoskeletal deformities but low statistical power for relative risks of 2 for rare conditions such as chromosomal abnormality or infant death.

Three types of analyses that compared reproductive outcomes to dioxin levels are presented here. Dioxin levels were measured in 1987, and in one analyses those measurements were used to estimate initial doses received in SEA. Current dioxin levels with adjustment for time since departure from SEA, and current categorized dioxin levels were used in the other two analyses.

Analyses of miscarriage, total adverse outcome, total conceptions, birth weight, birth defects, birth defect severity, specific birth defects, infant death and neonatal death were carried out on all conceptions and children and with restriction to full siblings (step-children were excluded) to minimize genetic variation. Additionally, all reproductive outcomes except sperm count, percent abnormal sperm and multiple birth defects were analyzed with and without consideration of the pre-SEA reproductive experiences of these men.

Verification of all live births and conceptions revealed that Ranch Hands and Comparisons misreported birth defects similarly. About 2% of all pre-SEA and post-SEA children had parent-reported birth defects that could not be verified. Both groups under-reported 7% of pre-SEA defects and 14% of post-SEA defects.

Semen

The association between the father's dioxin level and sperm count and the percentage of abnormal sperm was assessed based on semen specimens collected during the baseline examination in 1982. No significant association was found between dioxin and sperm count or the percentage of abnormal sperm.

Miscarriage, Total Adverse Outcome and Total Conceptions

Analyses of miscarriage adjusted for the outcomes of pre-SEA pregnancies were generally negative. Although miscarriages increased with dioxin in conceptions fathered by Ranch Hands with late tours, they decreased in those with early tours. Since it seems implausible that dioxin would act differently in the two groups, it is concluded that dioxin does not affect miscarriage rates. Furthermore, the highest number of post-SEA conceptions was found in Ranch Hands having the highest dioxin levels, which argues against a relationship between dioxin exposure and miscarriage.

Similar to the results obtain for miscarriage, the rate of adverse outcomes increased with dioxin in Ranch Hands with early tours and decreased in Ranch Hands with late tours. Like those for miscarriage, these findings don't make biologic sense and appear unrelated to dioxin.

Birth Weight

Analyses of birth weight with adjustment for birth weights of pre-SEA children were mostly negative. The few significant findings were not suggestive of a dioxin effect. Among pre-SEA children, the rate of abnormally low birth weight in children of Ranch Hands with the lowest dioxin levels (61.2 per 1000) was less than that in children of Comparisons (73.5 per 1000) and in

post-SEA children, the rate in Ranch Hand children (93.3 per 1000) was greater than that in children of Comparisons (41.9 per 1000). This change is due as much to the decrease in the Comparison rate as to the increase in the Ranch Hand rate.

Analyses of birth weight without statistical adjustment for birth weights of pre-SEA children were generally negative or were complicated by interactions with covariates that lack biological explanation. After restriction to full siblings, birth weight decreases with dioxin in some strata and increases in others, suggesting that these findings are chance occurrences. We find no evidence in these data to suggest that birth weight is adversely associated with the father's dioxin level.

Birth Defects

The significance of the association between paternal dioxin level and birth defects was assessed within each of 13 categories of anomalies (total congenital, nervous system, eye, ear face and neck, circulatory system and heart, respiratory system, digestive system, genital, urinary, musculoskeletal, skin, chromosomal and other unspecified). Analyses were first conducted on all children and then with restriction to full sibling children. Each analysis was carried out first without and then with adjustment for covariates.

Few significant associations were found. Those that were found did not appear consistently across analyses and most were not suggestive of a plausible dioxin effect. Some analyses of total congenital anomalies and musculoskeletal deformities found significant relative risks, but no consistent patterns emerged. For example, an analysis of total congenital anomalies found that children of Ranch Hand officers with low dioxin levels had a lower anomaly rate than children of Comparisons. Children of Ranch Hand enlisted flyers and enlisted ground personnel with low dioxin levels had higher rates than children of Comparisons, but the rates in children of fathers with the highest dioxin levels were not elevated. These findings are consistent with the conclusion that the apparent associations are chance occurrences and that there is no underlying association between paternal dioxin and birth defects.

Birth Defect Severity

No consistent pattern of association between birth defect severity and dioxin levels was found. For instance, in some analyses, the highest rates were found in children born to Ranch Hands with intermediate dioxin levels, while the lowest rates were found in children born to Ranch Hands with the highest dioxin levels. We conclude that there is no evidence in these data to suggest that dioxin is adversely associated with birth defect severity.

Specific Birth Defects and Developmental Anomalies

Twelve specific birth defects (anencephaly, spina bifida, hydrocephalus, cleft palate, cleft lip/palate, esophageal atresia, anorectal atresia, polydactyly, limb reduction defects, hypospadias, congenital hip dislocation, Down's syndrome) and 4 developmental anomalies (disturbance of emotion, hyperkinetic syndrome of childhood, specific delays in development, mental retardation) were investigated. Of these, there were only enough occurrences of specific delays in development and hyperkinetic syndrome of childhood to permit statistical analysis.

Analyses of hyperkinetic syndrome with pre-SEA adjustment were entirely negative. Two unadjusted analyses of specific delays in development found significant associations but these were not supportive of a hypothesis of adverse effects of dioxin. One of these findings was caused by decreasing rates with extrapolated initial dioxin. The other was due to high post-SEA rates in children of Ranch Hands with intermediate dioxin levels and lower rates in children of Ranch Hands with high dioxin levels. Analyses of hyperkinetic syndrome without pre-SEA adjustment found one significant association. This finding was caused by a decreasing rate with dioxin in children of Ranch Hands, a finding opposite to the expected dose-response and most likely due to chance. Analyses of specific delays in development without pre-SEA adjustment found one significant association, caused by the rate being higher in children of Ranch Hands with low dioxin levels than in children of Comparisons. The rate in children of Ranch Hands with high dioxin levels was not significantly different from the rate in children of Comparisons.

These findings are weak, inconsistent and often opposite to the expected dose response. They are not supportive of a hypothesis of an adverse association between dioxin and delays in development or hyperkinetic syndrome.

Multiple Birth Defects

Of 1772 post-SEA children included in these analyses, 57 had multiple defects that could not be attributed to recognized syndromes. The few significant associations with dioxin were caused by increased rates of multiple birth defects in children of Ranch Hands with low dioxin levels relative to children of Comparisons. The rates in children of Ranch Hands with the highest dioxin levels were not significantly elevated. These findings are weak and inconsistent with the expected dose-response. We conclude that there is no evidence in these data that dioxin is adversely associated with multiple birth defects.

Infant and Neonatal Mortality

Analyses of infant death were either negative or could not be carried out due to insufficient data. Analyses of neonatal death found two significant associations, both caused by the rate of neonatal death being lower in children of Ranch Hands with the highest dioxin levels than in children of Comparisons (opposite to the expected dose response). We conclude that there is no association between dioxin and infant or neonatal mortality.

Summary

Extensive analyses of verified birth defects and other reproductive outcomes were conducted with the father's serum dioxin level as the measure of exposure.

The lack of significant association between dioxin and total conceptions and between dioxin and any considered semen characteristic provide no support for the claim that Ranch Hand dioxin exposure is adversely related to the ability to father children. Similarly, the lack of association between dioxin and miscarriage, total adverse outcome, birth weight, any of 13 categories of birth defects and neonatal death provides no support for the idea that dioxin is adversely related to reproductive outcomes in this population.

The few positive associations found between dioxin and reproductive outcomes were generally weak, inconsistent or biologically implausible. These data provide no support for the hypothesis that paternal dioxin exposure is adversely associated with reproductive outcomes. Whether dioxin exposure of the mother before or during pregnancy results in abnormalities in the developing fetus or child could not be addressed in this study and remains an open question.

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